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6. AUTHOR(S)  Ramin B. Arami and M.B. Rao			
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## **A RESULT ON A 2x2 SURVIVAL EXPERIMENT**

**Ramin B. Arami and M.B. Rao**

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Center for Multivariate Analysis  
417 Thomas Building  
Penn State University  
University Park, PA 16802

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# A Result On A $2 \times 2$ Survival Experiment

Ramin B. Arani

Division of Biometry and Risk Assessment

National Center for Toxicological Research,

3900 NCTR Drive, Jefferson, Arkansas 72079-9502, USA

M. Bhaskara Rao

Department of Statistics, North Dakota State University

Fargo, North Dakota 58105, USA

## *Abstract*

Lifetime data classified according to categorical variables under the proportionality of the hazard functions of response variables for various treatment combinations is assumed. The proposed model is a combination of Cox's proportional hazards model and ANOVA model. The existence of a solution to the marginal likelihood function is examined for the case of  $2 \times 2$  two-way classification. We provide an easily verifiable condition for the existence of a unique estimate.

**Key Words:** Hazard function, Cox's Proportional Hazards model, Marginal likelihood, Convex hull.

## 1 Introduction

The Cox Proportional Hazards model<sup>1</sup> has enjoyed enormous popularity among statisticians for assessing the influence of various factors on survival time. The Science Citation Index indicates that by the end of 1993 there were over 7000 references to that article which makes it one of the most frequently cited articles, Henderson.<sup>2</sup> Let us look at the basic idea behind this model.

Let  $T_i (i = 1, \dots, n)$  be independent continuously distributed random variables representing the times of death of  $n$  individuals and suppose there exists a censoring time  $C_i$  associated with each individual. Under Cox's PH model, the  $i$ th individual hazard rate

$$\lambda_i(t) = \lim_{\delta \downarrow 0} \Pr[T_i \leq t + \delta | T_i \geq t]$$

is of the special form

$$\lambda_i(t) = \lambda_0(t) \exp(\beta' \mathbf{x}_i),$$

where  $\mathbf{x}_i$  is a column vector of  $p$  covariates,  $\beta'$  is the transpose vector of their corresponding unknown coefficients, and finally  $\lambda_0(t)$  represents a fixed unknown baseline hazard rate for individuals with  $\mathbf{x}$ . The observed data for the  $i$ th individual consist of  $\min(T_i, C_i)$ ,  $\delta_i = I(T_i \leq C_i)$  and  $\mathbf{x}_i$  where  $I(\cdot)$  is the indicator function. Furthermore, note that the probability density function (pdf) of  $T_i$  is uniquely determined by its hazard function as

$$f_i(t; \beta) = \lambda_0(t) \exp(\beta' \mathbf{x}'_i) \exp\left[-\exp(\beta' \mathbf{x}_i) \int_{(0,t]} \lambda_0(u) du\right], \quad t > 0.$$

The objective is to make inferences on the parameters of interest, namely  $\beta$ 's. If a functional form is assumed for  $\lambda_0(t)$ , one can rely on the maximum likelihood method of estimation and the corresponding asymptotic results to draw appropriate inferences. However, the maximum likelihood estimation of the parameters is fraught with many difficulties. Alternatively, if no functional form is assumed for  $\lambda_0(t)$ , one needs to rely on non-parametric techniques. Consequently, we require an estimating function that is purely a function of  $\beta$ 's. Thus, Cox<sup>1</sup> observed that distribution of the relative positions, *i.e.* ranks, of the observations is constant in time and furthermore is entirely a function of covariates. This is the nub of the marginal likelihood principle.

There are two ways of recording the relative positions in a given set of data. One way is to consider the rank of  $T_i$  which is  $R_i = \#\{1 \leq j \leq n : T_j \leq T_i\}$  and under the absolutely continuous assumption of  $T_i$ 's the ranks are a permutation of  $1, 2, \dots, n$  almost surely. Another way of identifying the location of the data is in terms of the label associated with  $i$ th order statistics, denoted by  $S_i$ . Note that the rank vector,  $\mathbf{R} = (R_1, R_2, \dots, R_n)$ , and the label vector,  $\mathbf{S} = (S_1, S_2, \dots, S_n)$ , determine each other

uniquely. As a matter of fact, the permutation  $\mathbf{R}$  is the inverse permutation of  $\mathbf{S}$  if we view  $\mathbf{R}$  and  $\mathbf{S}$  as maps from  $\{1,2,\dots,n\} \rightarrow \{1,2,\dots,n\}$ . More precisely,  $R_{S_1} = 1, R_{S_2} = 2, \dots, R_{S_n} = n$ .

We now focus on the distribution of  $\mathbf{R}$  or, equivalently that of  $\mathbf{S}$ . The number of possible values of  $\mathbf{R}$  is  $n!$ . Let  $\mathbf{r} = (r_1, r_2, \dots, r_n)$  be a permutation of  $1,2,\dots,n$  and  $\mathbf{s} = (s_1, s_2, \dots, s_n)$  be the inverse of  $\mathbf{r}$ . Let  $f_i(\cdot)$  be the pdf of  $T_i$ ,  $i = 1,2,\dots,n$ . Then,

$$P(\mathbf{R} = \mathbf{r}) = P(\mathbf{S} = \mathbf{s})$$

$$= \int_{0 < t_1 < \dots < t_n < \infty} \dots \int f_{s_1}(t_1) f_{s_2}(t_2) \dots f_{s_n}(t_n) dt_1 dt_2 \dots dt_n \quad (1)$$

$$= \prod_{i=1}^n \frac{\exp(\mathbf{x}'_{s_i} \beta)}{\sum_{j=i}^n \exp(\mathbf{x}'_{s_j} \beta)} = \prod_{i=1}^n \frac{\exp(\mathbf{x}'_{s_i} \beta)}{\sum_{j \in \mathfrak{R}(i)} \exp(\mathbf{x}'_{s_j} \beta)}$$

This probability also can be written in terms of the so-called *risk sets*  $\mathfrak{R}(i) = \{s_i, s_{i+1}, \dots, s_n\}$  which represents the set of individuals that are alive just before the  $i$ th death. The above probability is referred to as the marginal likelihood  $L_m(\cdot)$ . This approach was originally proposed by Cox<sup>1</sup> and further clarified by Cox,<sup>5</sup> and Kalbfleisch and Prentice,<sup>6</sup> and also discussed by Miller,<sup>7</sup> Lawless<sup>8</sup> and Cox and Oakes.<sup>9</sup> Realistically some observations could be censored, hence Equation (1) is modified by considering taking the product over the non-censored observations, *i.e.*, replacing  $n$  by total number of failures,  $k$ .

It should be noted that the Equation (1) can also be obtained through partial likelihood argument, see Andersen<sup>10</sup>. The maximum marginal likelihood estimators,  $\hat{\beta}$ , are the solution to the score equations generated by  $\nabla \log L_m(\beta) = 0$ . The estimators have been shown to be asymptotically normal with mean  $\beta_0$  and covariance matrix of  $\Sigma = \mathbf{I}_0^{-1}$  where  $\mathbf{I}_0 = -\nabla \cdot \nabla' \log L_m(\hat{\beta})$  is the observed information matrix and  $\nabla$  refers to the gradient vector operator.

In this paper, we explore the above model in the context of a  $2 \times 2$  classification which is one the most commonly used design scheme in cohort studies. Arani and Rao<sup>3</sup> provided a necessary and sufficient condition for the existence of a unique solution to likelihood equations in the case of  $2 \times 2$  classification design when the baseline hazard function corresponds to the exponential distribution. These conditions were derived by utilizing the results provided by Mäkeläinen *et al.*<sup>4</sup> In the next section, we provide a necessary and sufficient condition for existence of a unique maximum marginal (or partial) likelihood estimates, first for the case of single observation in each cell, followed by extension to multiple observations. Finally in the last section, the implementation of the results are illustrated through an example.

## 2 Existence of a Unique Solution

There is no guarantee that the maximum likelihood estimate based on the marginal likelihood of the ranks exists and is unique. Thus, before exploring the asymptotic properties of the estimator the question of existence and uniqueness must be resolved.

Note that Equation (1) can be rewritten as<sup>10</sup>

$$L_m(\beta) = \prod_{i=1}^k \left\{ 1 + \sum_{j \in \mathfrak{N}(i) - \{i\}} \exp((\mathbf{x}'_j - \mathbf{x}'_{s_i})\beta) \right\}^{-1}. \quad (2)$$

Jacobsen<sup>11,12</sup> showed  $L_m(\beta)$  is strictly concave if and only if the contrast covariate vectors,

$$\mathbf{x}'_j - \mathbf{x}'_{s_i}, \quad \text{for every } i = 1, 2, \dots, k \text{ and } j \in \mathfrak{N}(i) - \{i\}, \quad (3)$$

span the parameter space  $\Theta$ . Additionally, he showed that  $\hat{\beta}$  exists and is unique if and only if  $\mathbf{0}$  belongs to the interior of the convex hull of the contrast covariate vectors,  $\mathbf{x}'_j - \mathbf{x}'_{s_i}$ ,  $i = 1, 2, \dots, k$ , and  $j \in \mathfrak{N}(i) - \{i\}$ . (Note that the bold characters refer to vectors or matrices.)

First, let us consider the following  $2 \times 2$  design with single observation in each cell,

		Drug <i>B</i>	
		Dose Level	$b_1$
Drug <i>A</i>	$a_1$	$T_{11}$	$T_{12}$
	$a_2$	$T_{21}$	$T_{22}$

such that  $T_{ij}$  and  $\mathbf{x}_{ij}$  denote the lifetime and the covariate vector associated with the individual who has been administered the  $i$ th dose level of Drug *A* and the  $j$ th dose level of Drug *B*. The hazard function of  $T_{ij}$  is proposed to be

$$\lambda_{ij}(t) = \lambda_0(t) \exp(\alpha_i + \beta_j), \quad t > 0; \quad i = 1, 2 \text{ and } j = 1, 2$$

subject to  $\alpha_1 + \alpha_2 = 0$  and  $\beta_1 + \beta_2 = 0$ . These constraints are imposed to avoid any nonidentifiability problem. Thus, it suffices to estimate the parameter vector  $(\alpha_1, \beta_1)$ . Under the above design the covariate vectors,  $\mathbf{x}_{ij}$ , are identified to be  $\mathbf{x}'_{11} = (1,1)$ ,  $\mathbf{x}'_{12} = (1,-1)$ ,  $\mathbf{x}'_{21} = (-1,1)$  and  $\mathbf{x}'_{22} = (-1,-1)$ . For simplicity, let  $(\alpha_1, \beta_1) = (\alpha, \beta) = \beta'$  and label the indices  $(1,1)$ ,  $(1,2)$ ,  $(2,1)$  and  $(2,2)$  by 1, 2, 3, and 4, respectively.

Let us consider the ideal case of no censoring with no ties. Let  $R_1$  be the rank of  $T_{11}$ ,  $R_2$  the rank of  $T_{12}$ ,  $R_3$  the rank of  $T_{21}$ , and  $R_4$  the rank of  $T_{22}$ . Note that the rank vector  $\mathbf{R} = (R_1, R_2, R_3, R_4)$  can assume  $4! = 24$  possible values. For the purpose of illustration, let us examine the necessary and sufficient conditions for the existence of a unique estimate for the special case of  $\mathbf{R} = (1,3,4,2)$ , *i.e.*,  $\mathbf{S} = (1,4,2,3)$ . Thus, the risk sets are  $\mathfrak{R}(1) = \{1,4,2,3\}$ ,  $\mathfrak{R}(2) = \{4,2,3\}$ ,  $\mathfrak{R}(3) = \{2,3\}$  and  $\mathfrak{R}(4) = \{3\}$ . The contrast vectors are given by  $\mathbf{x}'_4 - \mathbf{x}'_1 = (-2,-2)$ ,  $\mathbf{x}'_2 - \mathbf{x}'_1 = (0,-2)$ ,  $\mathbf{x}'_3 - \mathbf{x}'_1 = (-2,0)$ ,  $\mathbf{x}'_2 - \mathbf{x}'_4 = (2,0)$ ,  $\mathbf{x}'_3 - \mathbf{x}'_4 = (0,2)$  and  $\mathbf{x}'_3 - \mathbf{x}'_2 = (-2,2)$ . Note that clearly the contrast vectors span the parameter space and further more the convex hull generated by them contains zero which are indicative of a unique solution to likelihood equations. Similarly for each case of  $\mathbf{R}$ , one can examine the necessary and sufficient conditions for the existence of a unique estimate of  $(\alpha, \beta)$ .

It is instructive to examine when we have solutions for certain trails of deaths, but not for others. The order in which the individuals die is the key to an understanding of this phenomenon. Following an exhaustive search, it can be established that the

only time the optimal estimates exist is when the trail of deaths always moves crosswise as shown in Figure 1.

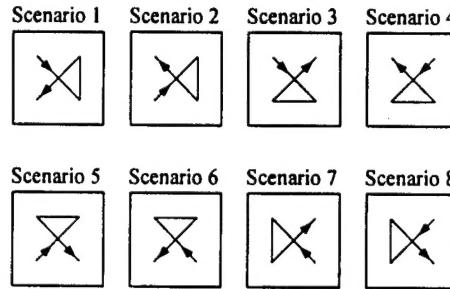


Figure 1. Trails of deaths under which estimator exist.

In all other scenarios, the trail of deaths moves either horizontally or vertically (*i.e.*, a zigzag pattern such as, the one corresponding to  $R = (2,4,1,3)$  ), which is not conducive to a unique solution of the marginal likelihood equations. Using Equation 1, probability of occurrence of each admissible scenario can be obtained, but for the sake of efficiency the algebraic detail is deferred to the appendix. Thus, It readily can be shown that a unique solution to likelihood equations exists with a positive probability of

$$P_0 = \sum_{m=1}^8 P(m\text{th scenario}) = \frac{1}{\sum_i w_i} \left( \sum_j \frac{1}{\sum_i w_i - w_j} \right) \quad (4)$$

where  $i, j = 1, \dots, 4$  and  $w_1 = \exp(\alpha + \beta)$ ,  $w_2 = \exp(\alpha - \beta)$ ,  $w_3 = \exp(-\alpha + \beta)$ , and  $w_4 = \exp(-\alpha - \beta)$ .

Up to this point, we assumed that all the failure times are observed (*i.e.*, censoring is not present) which might not be feasible. In the presence of censoring the same line of reasoning can be followed to establish easily the scenarios under which a unique solution exists. Let  $\Delta_{ij} = I(T_{ij} \leq C_{ij})$  be a Bernoulli random variable (as defined in Section 1) representing the censoring status of the individual who has received  $i$ th and  $j$ th dose level of Drug  $A$  and Drug  $B$ , respectively. All admissible scenarios for each possible value of  $\Delta_{\bullet\bullet} = \sum_i \sum_j \Delta_{ij} = 0,1,2,3,4$  are listed in Table 1,

and furthermore it follows that

$$P(\Delta_{\bullet\bullet} = 2) = \frac{2}{\sum_i w_i} \left( \sum_j \frac{1}{\sum_i w_i - w_j} \right) = 2P_0$$

and

$$P(\Delta_{\bullet\bullet} = 3) = 3P_0.$$

Furthermore, the above results are extended to the case of  $n_{ij}$  individuals in  $ij$ th cell in the following theorem. Letting  $T_{ijk}$  be the lifetime of the  $k$ th individual who has been administered  $i$ th dose level of Drug  $A$  and  $j$ th dose level of Drug  $B$ , where  $i = 1,2, \dots, I$ ,  $j = 1,2, \dots, J$  and  $k = 1,2, \dots, n_{ij}$  and  $n_{\bullet\bullet} = \sum_i \sum_j n_{ij}$  we have.

**Theorem** Let  $T_{ijk}$ , where  $i = 1,2, \dots, I$ ,  $j = 1,2, \dots, J$  and  $k = 1,2, \dots, n_{ij}$ , be independent positive random variables, and  $T_{(1)} < T_{(2)} < \dots < T_{(n_{\bullet\bullet})}$  be the corresponding order statistics. There exists a unique solution for the marginal likelihood equations, if

there exists  $s_1 < s_2 < s_3 < s_4$  such that  $T_{(s_1)} < T_{(s_2)} < T_{(s_3)} < T_{(s_4)}$  follows one of the schemes in Table 1.

*Proof:* Given  $T_{(s_1)} < T_{(s_2)} < T_{(s_3)} < T_{(s_4)}$  follows one of the admissible scenarios, without loss of generality first scenario is assumed, thus the labels of  $T_{(s_1)}$ ,  $T_{(s_2)}$ ,  $T_{(s_3)}$  and  $T_{(s_4)}$  are to be  $11k_1$ ,  $22k_2$ ,  $12k_3$  and  $21k_4$  respectively for some  $1 \leq k_1 \leq n_{11}$ ,  $1 \leq k_2 \leq n_{22}$ ,  $1 \leq k_3 \leq n_{12}$ , and  $1 \leq k_4 \leq n_{21}$ . The risk sets  $\mathfrak{R}(i_1)$ ,  $\mathfrak{R}(i_2)$   $\mathfrak{R}(i_3)$  and  $\mathfrak{R}(i_4)$  associated with the entire data and the risk sets  $\mathfrak{R}(1)$ ,  $\mathfrak{R}(2)$   $\mathfrak{R}(3)$  and  $\mathfrak{R}(4)$  associated with the particular segment

$A \cdot B$	$b_1$	$b_2$
$a_1$	$T_{11k_1}$	$T_{12k_3}$
$a_2$	$T_{21k_4}$	$T_{22k_2}$

of the data have the following relation  $\mathfrak{R}(r) \subset \mathfrak{R}(s_r)$  for  $r = 1, 2, 3, 4$ . Consequently, the contrast covariate vectors associated with the entire data set will contain the contrast covariate vectors associated with the above data segment. Afortiori, the marginal likelihood equations associated with the entire data are uniquely solvable in  $\beta$ .  $\square$

Further more defining,

$$A = \{\text{no admissible trail in any 4 adjacent positions}\}$$

$$B = \{\text{no admissible trail in any subsequence}\}.$$

It is followed that  $B \subseteq A$  and the following inequality follows immediately

$$P(B) \leq P(A) = (1 - 6P_0)^{(\sum_{ij} n_{ij}) - 3}.$$

Hence, a unique solution to the marginal likelihood equations exists with probability converging to 1 exponentially as  $\min_{i,j} n_{ij} \rightarrow \infty$ .

It should be noted that the above results were presented in the case with no censoring to preserve continuity in the text. Moreover, the results can be extended to case with censoring by replacing  $T_{ijk}$  with  $Y_{ijk} = \min(T_{ijk}, C_{ijk})$ .

### 3 Discussion

As noted earlier, the Cox's regression model is used frequently to analyze survival data augmented by some additional information. Naturally, this model has been incorporated in many software packages such as PHREG procedure in SAS. One practical advantage of the obtained results is that they can be utilized as a diagnostic tool to identify any unrealistic and misleading results. In situations with no admissible scenario, one can conclude inappropriateness of the proposed additive model or a need for additional observation to be taken. Clearly, in the case of historical data, second suggestion is not viable. Thus, alternative models need to be explored.

For the sake of illustration, we consider the data obtained by Edmunson *et al.*<sup>13</sup> for which the objective was to study the effect of two chemotherapy treatments, namely cyclophosphamide alone or its combination with adriamycin, after surgical treatment of ovarian cancer. A total of 26 women who had experienced surgical

excision of all tumor were considered. The patients were also classified according to whether residual disease was completely or partially excised. Patients were randomly assigned to one the chemotherapy treatments. The data can be classified according to levels of excision and treatment status as follow.

		cyclophosphamide	cyclophosphamide + adriamycin
		Partial excision	Complete excision
638,1106+,855+, 803+,448+	1227+,1129+,563,744+, 353,377+		
156,1040+,59,329,268, 431,115,477+	421+,769+,365,770+,475, 64,1206+		

**Figure 2.** Survival times after randomization to treatment, + represents Censored observation.

The trail of deaths according to their cell number for the above data set is

$$\begin{array}{ccccccccccccccccccccccc}
 \rightarrow & \times & \rightarrow & \circ & \rightarrow & \circ & \rightarrow & \times & \rightarrow & \circ & \rightarrow & \times & \rightarrow & \times & \rightarrow & \circ & \rightarrow & \times & \rightarrow \cdots \\
 & 2 & & 2 & & 2 & & 2 & & 3 & & 4 & & 3 & & 4 & & 2 & & 1 & & 4 & & 4 & & 2 & & 3 & \\
 & * & & & & & & & & * & & & & & & & & & & & ! & & & & & & & & & \\
 \rightarrow & \times & \rightarrow & \circ & \rightarrow \cdots \\
 & 1 & & 3 & & 4 & & 4 & & 1 & & 1 & & 2 & & 1 & & 3 & & 4 & & 3 & & & & & & & & \\
 \end{array}$$

Clearly one can find a subsequence (indicated by \*) that satisfies at least one of the admissible scenarios, in Figure 1 such as the Scenario 1. This result in some sense (since full likelihood is not used additional conditions are imposed) supports the results obtain by Arani and Rao<sup>3</sup> in the parametric case when the baseline hazard is assumed to be constant. That is, in addition to requiring the at least two observations

in the diagonal cells, certain order is imposed on the survival times. Thus, it is concluded that any estimate based on marginal (partial) likelihood can be trusted.

No. of Failure	$\Delta_{\infty} = 0$	$\Delta_{\infty} = 1$	$\Delta_{\infty} = 2$	$\Delta_{\infty} = 3$	$\Delta_{\infty} = 4$
	<i>None</i>	<i>None</i>	$\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $1 \ 4 \ 2 \ 3$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $1 \ 4 \ 3 \ 2$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $4 \ 1 \ 2 \ 3$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $4 \ 1 \ 3 \ 2$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $2 \ 3 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $2 \ 3 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $3 \ 2 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow o \rightarrow$ $3 \ 2 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow o \rightarrow$ $2 \ 3 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow x \rightarrow$ $2 \ 3 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow o \rightarrow$ $2 \ 3 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow x \rightarrow$ $2 \ 3 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow o \rightarrow$ $3 \ 2 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow x \rightarrow$ $3 \ 2 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow o \rightarrow x \rightarrow$ $3 \ 2 \ 4 \ 1$	$\rightarrow x \rightarrow x \rightarrow x \rightarrow o \rightarrow$ $1 \ 4 \ 2 \ 3$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $1 \ 4 \ 3 \ 2$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow o \rightarrow$ $4 \ 1 \ 2 \ 3$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $4 \ 1 \ 3 \ 2$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow o \rightarrow$ $2 \ 3 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $2 \ 3 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $3 \ 2 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $3 \ 2 \ 4 \ 1$	$\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $1 \ 4 \ 2 \ 3$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $1 \ 4 \ 3 \ 2$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $4 \ 1 \ 2 \ 3$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $4 \ 1 \ 3 \ 2$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $2 \ 3 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $2 \ 3 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $3 \ 2 \ 1 \ 4$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $3 \ 2 \ 4 \ 1$ $\rightarrow x \rightarrow x \rightarrow x \rightarrow x \rightarrow$ $3 \ 2 \ 4 \ 1$

**Table 1.** Admissible scenarios for which unique solution exists. Identify the subscripts 11 with 1, 12 with 2, 21 with 3, and 22 with 4, and deaths are marked by a cross  $\times$  and censoring by  $\circ$ .

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## Appendix

The details for obtaining Equation 4, is provided as follow. For the sake of simplicity, let us denote  $\theta = \exp(\alpha)$  and  $\varphi = \exp(\beta)$ . Thus using Equation 1, it follows.

$$\begin{aligned}
 P(\text{scenario 1}) &= P(\mathbf{R} = (1,3,4,2)) \\
 &= P(T_{11} < T_{22} < T_{12} < T_{21}) \\
 &= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\frac{\theta}{\varphi} + \frac{\varphi}{\theta}\right)\frac{\varphi}{\theta}}
 \end{aligned}$$

$$\begin{aligned}
 P(\text{scenario 2}) &= P(\mathbf{R} = (1,4,3,2)) \\
 &= P(T_{11} < T_{22} < T_{21} < T_{12}) \\
 &= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\frac{\theta}{\varphi} + \frac{\varphi}{\theta}\right)\frac{\theta}{\varphi}}
 \end{aligned}$$

$$\begin{aligned}
 P(\text{scenario 3}) &= P(\mathbf{R} = (3,1,2,4)) \\
 &= P(T_{12} < T_{21} < T_{11} < T_{22}) \\
 &= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{1}{\theta\varphi}\right)\frac{1}{\theta\varphi}}
 \end{aligned}$$

$$\begin{aligned}
 P(\text{scenario 4}) &= P(\mathbf{R} = (4,1,2,3)) \\
 &= P(T_{12} < T_{21} < T_{22} < T_{11}) \\
 &= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{1}{\theta\varphi}\right)\theta\varphi}
 \end{aligned}$$

$$\begin{aligned}
P(\text{scenario 5}) &= P(\mathbf{R} = (3,2,1,4)) \\
&= P(T_{21} < T_{12} < T_{11} < T_{22}) \\
&= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{1}{\theta\varphi}\right)\frac{1}{\theta\varphi}}
\end{aligned}$$

$$\begin{aligned}
P(\text{scenario 6}) &= P(\mathbf{R} = (4,2,1,3)) \\
&= P(T_{21} < T_{12} < T_{22} < T_{11}) \\
&= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{1}{\theta\varphi}\right)\theta\varphi}
\end{aligned}$$

$$\begin{aligned}
P(\text{scenario 7}) &= P(\mathbf{R} = (2,3,4,1)) \\
&= P(T_{22} < T_{11} < T_{12} < T_{21}) \\
&= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta}\right)\left(\frac{\theta}{\varphi} + \frac{\varphi}{\theta}\right)\frac{\varphi}{\theta}}
\end{aligned}$$

$$\begin{aligned}
P(\text{scenario 8}) &= P(\mathbf{R} = (2,3,4,1)) \\
&= P(T_{22} < T_{11} < T_{21} < T_{12}) \\
&= \frac{1}{\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta} + \frac{1}{\theta\varphi}\right)\left(\theta\varphi + \frac{\theta}{\varphi} + \frac{\varphi}{\theta}\right)\left(\frac{\theta}{\varphi} + \frac{\varphi}{\theta}\right)\frac{\theta}{\varphi}}
\end{aligned}$$

Note that summing up the above probabilities would result in Equation 4. Similarly, one can obtain the probability of admissible scenarios under censoring.

## References

1. Cox, D. R. 'Regression models and life tables', *J.R.Stat.Soc., Series B*, **34**, 187-220 (1972).
2. Henderson, R. 'Problem and prediction in survival-data analysis', *Statistics in Medicine*, **14**, 161-184 (1995).
3. Arani, R. B. and Rao, M. B. 'A note on existence of maximum likelihood estimators in the framework of proportional hazards and categorical variables', (submitted manuscript) (1995).
4. Mäkeläinen, T., Schmidt, K., and Styan, G. P. H. 'On the existence and uniqueness of the maximum likelihood estimate of a vector-valued parameter in fixed-size samples', *Ann. of Statistics*, **9**, 4, 758-767 (1981).
5. Cox, D. R. 'Partial likelihood', *Biometrika*, **62**, 2, 269-276 (1975).
6. Kalbfleisch, J D., and Prentice, R. L. *The statistical analysis of failure time data*, Wiley , New York, 1980.
7. Miller, R. G. *Survival Analysis*, Wiley, New York 1981.
8. Lawless, J. F. *Statistical Models for Lifetime Data*, Wiley , New York, 1982.
9. Cox, D. R., and Oakes, D. *Analysis of survival data*, Chapman and Hall, London, 1984.
10. Andersen, P. K., Borgan O., Gill, R .D., and Keiding, N. *Statistical models based on counting process*, Springer-Verlag, New York 1993.
11. Jacobsen, M. 'Existence and unicity of MLEs in discrete exponential family distributions', *Scand. J. Statist.*, **16**, 335-349 (1989a).
12. Jacobsen, M. 'Right censoring and martingale methods for failure time data', *Ann. Statistics*, **17**, 1133-1156 (1989b).
13. Edmundon, J.H., Fleming, T.R., Decker, D.G., Malkasian, G.D., Jorgenson, E.O., Jeffries, J.A., Webb, M.J. and kvols, L.K. 'Different Chemotherapeutic sensitivities and host factors affecting prognosis in advanced ovarian carcinoma versus minimal residual disease', *Cancer Treatment Report*, **63**, 241-247 (1979).